The Report Committee for Ashlee Beth Mitchell von Buttlar
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Cerebellar Tumor Location as a Predictor of Neurocognitive Functioning Among Survivors of Pediatric Brain Tumors

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Douglas Greg Allen, Supervisor

Emily Strassner Greenspahn, Co-Supervisor

Cerebellar Tumor Location as a Predictor of Neurocognitive Functioning Among Survivors of Pediatric Brain Tumors

by

Ashlee Beth Mitchell von Buttlar, B.S., B.A.

Report

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Abstract

Cerebellar Tumor Location as a Predictor of Neurocognitive Functioning Among Survivors of Pediatric Brain Tumors

Ashlee Beth Mitchell von Buttlar, M.A.

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Supervisor: Douglas Greg Allen

The literature has clearly demonstrated that the cerebellum serves as a major processing center in the brain for many complex functional pathways ranging from attention and learning to emotions and affect. Research is now emphasizing the importance of connectivity between the cerebellum and other brain regions, and has begun highlighting the need to understand the impact of damage to distinct regions on functional pathways throughout the brain. One particular type of cerebellar damage, caused by posterior fossa tumors, has received substantial attention in the medical and neuropsychological literature in recent years.

Tumors of the posterior fossa, which includes the cerebellum and brain stem structures, account for over 15% of brain tumors in children (Ostrom et al., 2015). Due to advances in treatment, survival rates have increased dramatically for individuals with posterior fossa tumors, leading to a greater need for long-term medical and psychosocial care (Beebe et al., 2005; Fisher et al., 2008; Gnekow et al., 2012). Treatments for these tumors, including chemotherapy and cranial radiation, are known to produce long-term

deficits in a variety of neurocognitive domains (Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). These deficits are referred to as "neurocognitive late effects," and can be seen as impaired performance in the areas of attention, memory, executive functioning, visual-spatial processing, and processing speed (Askins & Moore, 2008; Conklin et al., 2012; Shortman et al., 2014). Neurocognitive late effects can be especially pronounced in patients with localized cranial radiation, as is common with malignant brain tumors (Askins & Moore, 2008).

Research has clearly shown that different regions of the cerebellum uniquely contribute to various neurocognitive functions (Stoodley & Schmahmann, 2009). Additionally, much research has assessed the neurocognitive implications of posterior fossa tumors in children. However, little work has examined the unique relationship between specific tumor locations within the cerebellum and later neurocognitive outcomes. The purpose of this study is to determine whether the particular location of tumors in the cerebellum can predict neurocognitive functioning in the domains of attention and executive functioning in children with these tumors.

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INTRODUCTION

The theory that the cerebellum, a region at the base of the brain near the brain stem, is involved in more complex processes than simply motor control and coordination has been present in the literature for decades. However, the knowledge that the cerebellum serves as a major processing center in the brain for complex functional pathways ranging from attention and learning to emotions and affect has only recently become more widely accepted. Research is now emphasizing the importance of connectivity between the cerebellum and other brain regions, and has begun highlighting the need to understand the impact of damage to distinct regions on functional pathways throughout the brain. One particular type of cerebellar damage, caused by posterior fossa tumors, has received substantial attention in the medical and neuropsychological literature in recent years.

Tumors of the posterior fossa, which includes the cerebellum and brain stem structures, account for over 15% of brain tumors in children (Ostrom et al., 2015). Brain tumors in general, though rare, represent about 20% of all childhood cancers and are the most common form of cancer in children aged 19 and under in the United States (Ostrom et al., 2015). Due to advances in treatment, survival rates have increased dramatically for individuals with posterior fossa tumors (Beebe et al., 2005; Fisher et al., 2008; Gnekow et al., 2012; Ostrom et al., 2015; Palmer, 2008). Treatment protocols for these tumors vary widely based on tumor type, but typically include tumor resection that is often accompanied by cranial radiation and chemotherapy. These treatments have been shown to produce long-term deficits in a variety of neurocognitive domains (Grill et al., 1999;

Mulhern et al., 2000; Palmer et al., 2003; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). These deficits are collectively referred to as "neurocognitive late effects," and can be seen as deficits in the areas of attention, working memory, verbal memory, executive function, visual-spatial processing, and processing speed (Askins & Moore, 2008; Conklin et al., 2012; Shortman et al., 2014). Neurocognitive late effects can be especially pronounced in patients with localized cranial radiation, as is common with malignant brain tumors (Askins & Moore, 2008).

Research has clearly shown that different regions of the cerebellum uniquely contribute to various neurocognitive functions (Stoodley & Schmahmann, 2009). Additionally, much research has assessed the neurocognitive implications of posterior fossa tumors in children. However, little work has examined the unique relationship between specific tumor locations within the cerebellum and later neurocognitive outcomes. The purpose of this study is to determine whether the particular location of tumors in the cerebellum can predict neurocognitive functioning in the domains of attention and executive functioning in children with these tumors. It is hypothesized that cerebellar brain tumor location (right hemisphere, left hemisphere, vermis) and position (anterior, posterior) will explain a significant amount of variance in performance on tasks of attention and executive functioning.

INTEGRATIVE ANALYSIS

Cerebellar Anatomy and Functions

BASIC ANATOMY

Although the cerebellum accounts for only around 10% of the brain's volume, it contains over half of the total neurons in the brain (Azevedo et al., 2009). Interestingly, it also contains some of the smallest and the largest neurons in the brain (Standring, 2015). It is located dorsal to the pons and medulla, and is connected to the rest of the brain by three pairs of cerebellar peduncles. The fourth ventricle, a fluid-filled cavity, rests between the cerebellum and the pons and medulla.

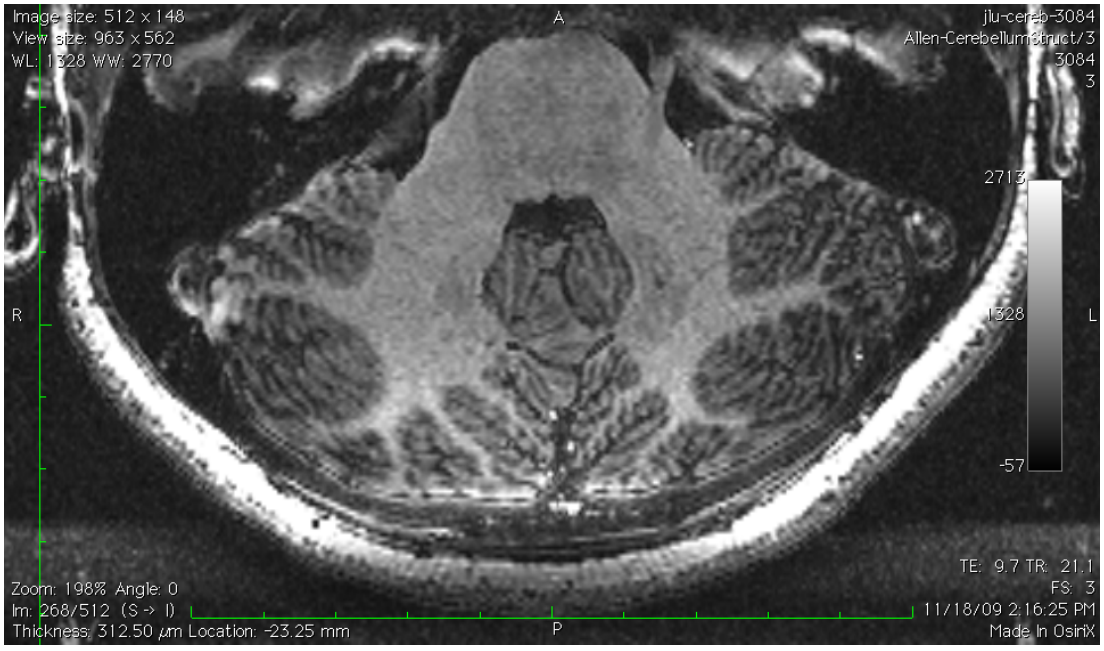

Figure 1: Axial image of the cerebellar hemispheres (lateral) and the cerebellar vermis (medial). Image reproduced with permission from Greg Allen, Ph.D.

The cerebellum consists of a gray matter cortex, which contains numerous grooves and folds, overlying a central white matter. These grooves and folds are highly convoluted, forming lobes and lobules that can be further subdivided by small fissures into folia (Arunakaran, 2012). This organization allows for the dense packing of neurons into the relatively small space in the skull occupied by the cerebellum. Located within the white matter are the four deep cerebellar nuclei, which are distinct cell bodies made up of gray matter that facilitate the transmission of afferent and efferent nerve impulses to and from various parts of the brainstem and cerebral cortex (Arunakaran, 2012). The dentate nucleus in particular has been the focus of many studies due to its large size, its lateral location within the cerebellar hemispheres, and its known role in aiding the transfer of information from the cerebellum to frontal and parietal brain regions (Akshoomoff & Courchesne, 1992; Allen et al., 2005; Quintero-Gallego, Gómez, Morales, & Márquez, 2011; Vaquero, Gómez, Quintero, González-Rosa, & Márquez, 2008).

There are four major types of neurons in the cerebellar cortex: granule, Purkinje, Golgi, and basket cells. Of these four cell types, Purkinje cells and granule cells play the most dominant roles in the transmission of nerve impulses, with Purkinje cells serving as the only output neurons to the cerebellar cortex, projecting to the deep cerebellar nuclei, which then project to the rest of the brain (Standring, 2015). The cerebellum also contains three distinct types of axons, the mossy, climbing, and parallel fibers, which project to and from the various cerebellar neurons and nuclei. The cerebellar cortex is modularly organized in a pattern of parallel "longitudinal zones" that project to particular regions of the deep cerebellar nuclei (Voogd & Glickstein, 1998). The microanatomy of the cerebellum is beyond the scope of this document, but a more detailed consideration of the cellular structure of the cerebellum can be found in *Gray's Anatomy* (Standring, 2015).

Anatomically, the cerebellum consists of three major lobes: the anterior lobe, the posterior lobe, and the flocculonodular lobe. The cerebellar vermis is located in the medial zone of the cerebellum, encompassed laterally by the cerebellar hemispheres and posteriorly by the flocculonodular lobe. This group of structures is collectively referred to as the corpus cerebelli. The primary fissure divides the corpus cerebelli into the anterior and posterior lobes (Arunakaran, 2012). The paramedian fissure separates the cerebellar hemispheres from the vermis, and the posterolateral fissure separates the flocculonodular lobe from the corpus cerebelli (Standring, 2015). The vermis can be further subdivided into nine distinct lobules that are closely associated with all regions of the cerebellar cortex. Lobules I through V are considered part of the anterior vermis, and lobules VI through IX are considered part of the posterior vermis (O'Halloran, Kinsella, & Storey, 2012).

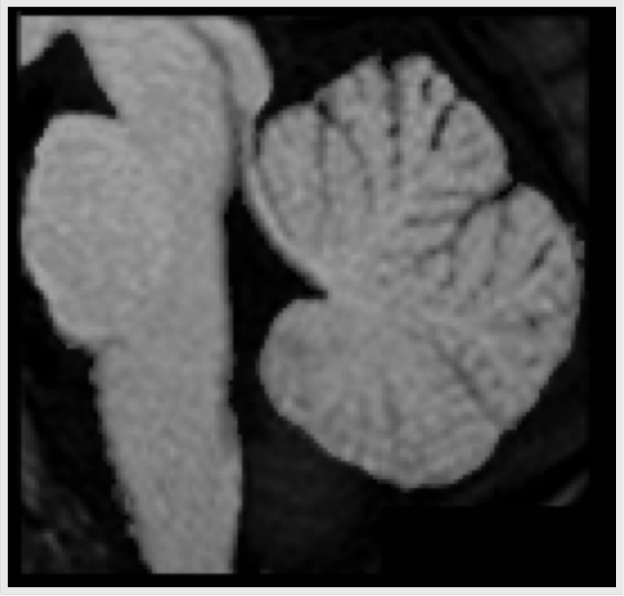

Figure 2: Saggital MRI image of the brainstem and cerebellar hemisphere. The primary fissure is clearly visible as indicated by the arrow. Image reproduced with permission from Greg Allen, Ph.D.

FUNCTIONAL NEUROANATOMY

There are various criteria to define the sub-regions of the cerebellum, though there is substantial overlap between different approaches (Barlow, 2002). One such approach is functional in nature, and determines cerebellar subdivisions based on functional connectivity and the functional role of each region. This approach leads to three motor sub-regions: (a) the vestibulocerebellum, which includes the flocculonodular lobe and is involved in functions such as balance and eye movements, (b) the spinocerebellum, which includes the vermis and adjacent parts of the cerebellar hemispheres and is concerned with regulating limb movements and proprioception, and (c) the cerebrocerebellum (also known as the pontocerebellum), which includes the lateral cerebellar hemispheres and is involved in motor planning and timing but has also been implicated in cognitive functioning (Allen et al., 2011). The cerebrocerebellum includes the dentate nucleus, which, as mentioned above, has many functional connections to frontal brain regions.

Cerebellar connections to and from the cerebral cortex can be classified as either afferent or efferent. The afferent system involves projections of cortical information to the cerebellum via the pontine nuclei in the pons, known as the ponto-cerebellar tracts (O'Halloran et al., 2012). The cerebello-thalamo-cortical pathway is the primary efferent pathway from the cerebellum to the frontal cortex, which goes from the dentate nucleus to thalamic nuclei via the cerebellar peduncles and midbrain, and then terminates in both motor and nonmotor areas of the contralateral frontal lobe. A schematic representation of these pathways is presented in Figure 3.

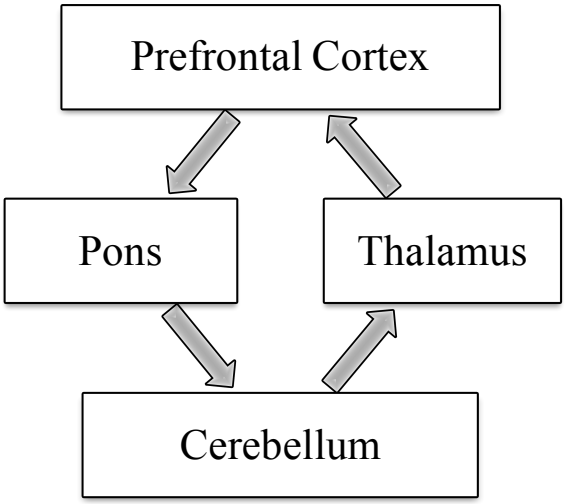

Figure 3: Schematic representation of ponto-cerebellar and cerebello-thalamo-cortical pathways.

The cerebellum has traditionally been studied for its contributions to motor functioning, but much research has also implicated the cerebellum in many non-motor functions (Allen, Buxton, Wong, & Courchesne, 1997; Schmahmann & Pandya, 2008; Stoodley, Valera, & Schmahmann, 2012). Functional connectivity studies in primates have demonstrated that the cerebellum receives inputs from many brain regions involved in cognition and emotion including the hypothalamus, parrahippocampal gyrus, cingulate gyrus, prefrontal cortex, and more (Allen et al., 2011). Similar research has uncovered functional outputs from the cerebellum to the contralateral prefrontal cortex in primates (Middleton & Strick, 2001). These connections have also been demonstrated in more recent studies of human cerebellar connectivity (Allen et al., 2005). Additionally, each of the areas involved in the cerebello-thalamo-cortical pathway (the cerebellum, the thalamus, and the prefrontal cortex) have been implicated in higher order cognitive and executive functions (Allen et al., 2005; Puget et al., 2009; Stoodley et al., 2012). Functional neuroimaging studies have also provided more evidence to suggest cerebellar involvement

in cognitive functions in both healthy individuals and individuals with cerebellar damage (Allen et al., 1997; Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013; Stoodley & Schmahmann, 2009; Stoodley et al., 2012).

Studies of individuals with acquired cerebellar damage have also provided more evidence for a cerebellar role in cognition and emotion. Decades of research on patients with cerebellar brain tumors reveals clear non-motor deficits present in this population, such as deficits in visuospatial, language, and executive functioning as well as transient personality changes (Catsman-Berrevoets & Aarsen, 2010; De Smet et al., 2009; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Palmer et al., 2010; Riva & Giorgi, 2000; Schmahmann & Sherman, 1998). Not all patients with cerebellar damage develop these neurocognitive sequelae, suggesting that damage to different cerebellar regions may lead to different outcomes, thus highlighting the need for more research in this area.

Despite the substantial amount of research on the cerebellum's contributions to motor and non-motor functions in humans as well as other mammals, much of the cerebellum's anatomy and functionality is still not fully understood. For instance, it is unclear whether anatomical boundaries defined by the molecular organization of the cerebellum fully align with functional boundaries (Apps & Hawkes, 2009). Additionally, Apps & Hawkes (2009) note that the lack of consensus in the field on terminology, as well as the molecular and functional organization of the cerebellum, has led to some difficulty in creating a unified "map" of the cerebellar cortex. These limitations have created challenges in gaining a deeper understanding of the links between the cerebellum and complex human behavior.

Although many studies have suggested a true non-motor role for the cerebellum, some other research has attempted to provide alternative explanations for these findings. Namely, some scientists have suggested that methodological flaws and/or eye movements

that are unaccounted for in some tasks considered by researchers to be motor-independent have overestimated the role of the cerebellum in higher cognition (Glickstein & Doron, 2008). However, the research highlighted above, as well as countless other studies, has clearly linked cerebellar damage to predictable affective and behavioral disturbances (Ramnani, 2011). Thus, it is clear that cerebellar damage leads to functionally significant impairments not just in movement but also affect and cognition. As such, studies of patients with cerebellar damage such as brain tumors continue to be vital in advancing our understanding of the contributions of the cerebellum to human behavior.

Pediatric Cerebellar Brain Tumors

Prevalence and Characteristics

Although rare, childhood cancers are not uncommon and impact a substantial number of children and families in the United States each year. A child born in the United States has an approximately 0.35% chance of being diagnosed with cancer before their 20th birthday, which equates to approximately 1 in 285 children under 20 years old receiving a cancer diagnosis (Ward, Desantis, Robbins, Kohler, & Jemal, 2014). Cancers are the second most common cause of death in children between the ages of 5 and 14, second only to accidents (Murphy, Xu, & Kochanek, 2013).

Statistics on different cancers show large variations depending on age and cancer type, with some cancers occurring much more commonly in childhood than others. Estimates vary as to which childhood cancers are most prevalent, with some data sets indicating that brain tumors are the most common form of cancer in children aged 0 to 19 (Ostrom et al., 2015) and others suggesting leukemia is the most common (Ward et al., 2014). However, many statistics on childhood cancers overall include only malignant brain tumors in their comparisons. Estimates for cancers among children aged 0 to 19 years old that include both benign and malignant brain and CNS tumors cite an incidence rate of approximately 5.57 per 100,000, and cite an incidence rate of 4.53 per 100,000 for leukemia (Ostrom et al., 2015). Regardless, brain and CNS tumors are considered to be the second most common cause of cancer-related death in children under the age of 19 (Ostrom et al., 2015).

According to the most recent statistical reports of brain tumors in the United States, tumors of the cerebellum account for approximately 16% of all brain tumors in childhood and adolescence, and comprise the largest proportion (nearly 19%) of all brain tumors in children 14 and under (Ostrom et al., 2015). Brain and CNS tumors have an average annual

age adjusted mortality rate of 5.78 per 100,000 (Ostrom et al., 2015). There are three main types of pediatric cerebellar tumors: (a) cerebellar astrocytomas, (b) medulloblastomas, and (c) ependymomas. However, ependymomas are quite rare, and commonly present in the brainstem rather than the cerebellum. Thus, for the purpose of this study, only cerebellar astrocytomas and medulloblastomas will be discussed.

Pediatric cerebellar astrocytomas (CAs) are some of the most common CNS tumors in children. The majority of these tend to be benign and low-grade, accounting for 25-35% of all pediatric posterior fossa tumors (Bonfield & Steinbok, 2015). Though there are different classes of CAs, they most commonly present as slow-growing pilocytic astrocytomas (approximately 75% of cases), with a peak incidence between 6 and 8 years of age (Bonfield & Steinbok, 2015). Common early symptoms of CA include headaches, especially headaches due to increased intracranial pressure (often a symptom of hydrocephalus, or a buildup of cerebrospinal fluid in the brain), neck stiffness, vomiting, lethargy, motor ataxia, and behavioral changes, though these symptoms vary depending on the size of the tumor (Bonfield & Steinbok, 2015; Ilgrenl & Stiller, 1987). Survival rates for CAs are relatively high, with estimates at or above 90% in the majority of cases (Beebe et al., 2005; Vaquero et al., 2008).

Medulloblastomas (MBs) are tumors that frequently arise from embryonal cells, which are embryonic cells that remain in the brain after birth. Embryonal tumors account for approximately 11% of brain tumors in children under the age of 20, and MBs account for approximately 64% of all embryonal tumors in this population (Ostrom et al., 2015). MBs, which are typically malignant and invasive, are more common in children under 10 years of age, with a peak incidence at around 5 years of age (Palmer, 2008; Ward et al., 2014). MBs can arise in any part of the cerebellum, though they commonly present in the vermis (Palmer, Reddick, & Gajjar, 2007). Symptoms of MB are similar to those of CA,

and include headache, lethargy, and vomiting, likely due to increased intracranial pressure (Palmer et al., 2007). Five-year survival rates range from 70-85% (Ostrom et al., 2015; Palmer, 2008).

TREATMENT FOR CEREBELLAR TUMORS

The treatment protocols for cerebellar tumors vary based on the type of tumor, tumor grade, tumor location, and several other factors including a patient's age and the presence of complicating conditions such as hydrocephalus. Surgery is typically the first step in treatment for cerebellar tumors, with the goal of resecting as much of the tumor as possible without damaging surrounding brain structures. CAs are often resolved through resection alone, but many MBs require resection, cranial-spinal radiation, and an additional dose of radiation directly to the posterior fossa. Some children with MB also require treatment with chemotherapy (Aarsen et al., 2009; Spiegler et al., 2004).

Advances in treatment have raised 5-year survival rates for children with MB to between 70% and 85%, and have raised 5-year survival rates for low-grade CA with total resection to between 90% and 100% (Fisher et al., 2008; Gnekow et al., 2012; Lassaletta, Bouffet, Mabbott, & Kulkarni, 2015; Schreiber et al., 2014; Villarejo, Diego, & Riva, 2007; Wisoff et al., 2011). However, they also introduce a host of adverse effects on many of the body's functional systems including the endocrine, skeletal, and central nervous systems. The patterns of deficits in intellectual, academic, and neuropsychological functioning following cancer treatments such as cranial radiation and chemotherapy are collectively known as "neurocognitive late effects".

Neurocognitive Late Effects of Treatment

In general, cancer treatments tend to impact neurocognitive functioning most in the domains of attention, executive functioning, visuospatial processing, processing speed,

working memory, and the ability to learn (Askins & Moore, 2008; Lassaletta et al., 2015). More specific declines in neurocognitive functioning vary widely based on the type of treatment a child receives, their specific cancer diagnosis, and several other variables that will be discussed below. In general, it is well documented that children with brain tumors show significant declines in neurocognitive functioning and academic achievement over time secondary to their tumors and subsequent treatments (Moore, 2005; Palmer et al., 2007). It is important to note, however, that not all children receiving similar treatments will show the same rates of neurocognitive morbidity, and thus it is likely a combination of many variables that ultimately contribute to neurocognitive vulnerability.

Much research suggests that cranial radiation can lead to significant neurocognitive impairments. There is a general consensus in the literature that exposure to cranial radiation is a major cause of adverse neurocognitive outcomes in children treated for brain tumors (Copeland, deMoor, Moore, & Ater, 1999; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Robinson et al., 2013; Spiegler et al., 2004). Research documenting the degree of neurocognitive late effects secondary only to chemotherapy without cranial radiation exposure has been somewhat inconsistent. Some research on children with acute lymphoblastic leukemia (ALL) has suggested that chemotherapy alone produces far fewer neurocognitive late effects than cranial radiation. Specifically, in a review on neurocognitive outcomes in children with ALL, Moleski (2000) concluded that intrathecal chemotherapy does have a negative impact on cognitive outcomes, but that these deficits are much less severe than the effects of cranial radiation therapy. A longitudinal study of 99 survivors of cancer (largely ALL and lymphoma) who were treated with either intrathecal chemotherapy or no CNS therapy found that patients' mean scores on neuropsychological assessments were within the average range, but the chemotherapy group had poorer performance, suggesting that chemotherapy has only a slight effect on

neurocognitive functioning (Copeland, Moore, Francis, Jaffe, & Culbert, 1996). Other studies have concluded that a large number of individuals treated with intrathecal chemotherapy show deficits in at least one domain of neurocognitive functioning (Moleski, 2000; Peterson et al., 2008). Many of these studies have focused on children with ALL or other types of cancer, as it is difficult to replicate these results with brain tumor patients given the frequent necessity of cranial radiation combined with chemotherapy as a part of treatment. However, as with cranial radiation, younger age at diagnosis tends to correlate with higher rates of cognitive deficits for intrathecal chemotherapy (Askins & Moore, 2008; Copeland et al., 1996; von der Weid et al., 2003).

Although researchers do not fully understand all of the mechanisms contributing to neurocognitive decline after cancer treatment, it has been suggested that decreases in the brain's gray and white matter after cranial radiation and/or chemotherapy may play a role (Mulhern et al., 2000; Reddick et al., 2000; Steen et al., 2001). Because human brains are rapidly developing throughout childhood and into early adulthood, exposure to neurotoxic agents in early childhood can directly impact cognitive development. White matter, which is made up of myelinated axons that promote rapid and automatic transmission of electrical impulses in the brain, is vital to human cognition as it allows for communication between various parts of the peripheral and central nervous systems. Exposure to cranial radiation has been linked to decreases in white matter volume and demyelination due to increased vascularization in the brain in children and young adults (Reddick et al., 2000; Schultheiss, Kun, Ang, & Stephens, 1995). Additionally, exposure to chemotherapy in childhood has been shown to contribute to changes in white matter in children with ALL and non-Hodgkin's lymphoma (Morioka et al., 2013; Wilson et al., 1991).

Predictors of Neurocognitive Late Effects

There are several variables associated with increased risk of neurocognitive deficits after treatment with cranial radiation therapy and chemotherapy. The most consistent factor implicated in poorer neurocognitive and academic outcomes for children with cancer is young age at diagnosis and subsequent exposure to neurotoxic treatments, especially cranial radiation (Aarsen et al., 2009; Askins & Moore, 2008; Brinkman et al., 2012; Copeland et al., 1999; Davis, Pitchford, Jaspan, McArthur, & Walker, 2010; Knight et al., 2014; Palmer et al., 2013; Schreiber et al., 2014). Copeland et al. (1999) used growth curve analysis to show that children with cerebellar tumors that did not receive cranial radiation therapy had more positive neurocognitive outcomes. Research has also linked higher doses of radiation to greater declines in neurocognitive functioning (Grill et al., 1999; Ris et al., 2001). A study by Spiegler et al. (2004) found a steeper decline in IQ shortly after cranial radiation, suggesting time since diagnosis may be an important variable when evaluating neurocognitive functioning after tumor treatment with cranial radiation. A regression model also indicated a decreased rate of decline in cognitive functioning as the time from diagnosis increased, indicating attenuating decline in IQ over time (Spiegler et al., 2004).

The literature remains inconsistent as to whether or not biological sex is an important factor in predicting neurocognitive declines secondary to cancer treatments. Some studies have suggested sex is related to differential outcomes, typically indicating poorer neurocognitive outcomes for females treated for cerebellar tumors (Nagel et al., 2006; Palmer et al., 2003, 2013). However, other research has found no sex-related differences in patient outcomes (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Knight et al., 2014; Schreiber et al., 2014). Thus, it is unclear as to whether sex is an important predictor of neurocognitive functioning after cancer treatments.

It is important to note that the potential for neurocognitive changes following treatment is increased in children with brain tumors due to the fact that the cancerous cells arise in the brain, and thus have a greater likelihood of directly impacting neurocognitive functions. This is true even prior to the introduction of damaging treatments such as cranial radiation and chemotherapy. Ultimately, these neurocognitive sequelae can lead children to have diminished performance in the domains of IQ and academic achievement relative to their peers, with this gap widening as time elapses potentially due to a decreased rate of skill development for tumor survivors over time (Knight et al., 2014; Palmer et al., 2013; Papazoglou, King, Morris, & Krawiecki, 2008; Reeves et al., 2006; Spiegler et al., 2004). Additionally, cerebellar tumors and their treatment can have serious long-term functional consequences for children, including problems related to relationships, school, and emotional functioning (Aarsen et al., 2006).

Domains of Neurocognitive Functioning

Neurocognitive functioning is a broad term that encompasses a variety of domains including, but not limited to, intellectual functioning, memory, attention, executive functioning, motor skills, and visuospatial skills. These domains can be measured with a wide range of neuropsychological tests, and damage to certain neural pathways in the brain can lead to deficits in many of these skills. For the purpose of this study, two domains of neurocognitive functioning, attention and executive functioning, will be considered.

ATTENTION

The domain of attention can be conceptualized in various ways, though it most often includes the subdomains of selective attention, sustained attention, divided attention, and shifting attention (Baron, 2004; Ginstfeldt & Emanuelson, 2010; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Selective attention refers to one's ability to focus on a target cognitive set or stimulus, especially in the presence of distraction (Baron, 2004; Ginstfeldt & Emanuelson, 2010). Common tools used to assess selective attention include sequential digit span tasks. Sustained attention is conceptualized as an individual's ability to maintain focus and respond consistently over a period of time during repetitive or continuous tasks (Baron, 2004). Continuous performance tests are often used to assess sustained attention, which require an individual to respond to a target stimulus (visual or verbal) over a prolonged period of time. Divided attention refers to an individual's ability to perform multiple tasks or respond to multiple events simultaneously (Baron, 2004). Tests of divided attention could include tasks that require an individual to simultaneously attend to both verbal and visual stimuli, or require an individual to attend to two different types of target stimuli at the same time (such as numbers and letters). Shifting attention refers to one's ability to flexibly shift focus from one stimulus to another (Baron, 2004).

Commonly used tests of shifting attention include verbal or visual fluency tests, or tests that have task "rules" an individual must follow that change regularly (Ginstfeldt & Emanuelson, 2010).

EXECUTIVE FUNCTIONING

Executive functioning (EF) is an umbrella term that is often used within the field of psychology to refer to a range of higher-order cognitive functions related to goal-directed behavior (V. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Many different models of EF have been proposed, though no model has received universal acceptance in the field of neuropsychology. Most models propose that EF involves several subcomponents, including planning, cognitive flexibility, reasoning, inhibition, initiation, and working memory (P. Anderson, 2002). Research has also demonstrated a clear link between intellectual functioning and EF, as well as with other domains of neurocognitive functioning (V. Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Gilbert & Burgess, 2008). Regardless of the model utilized, it is clear that EF abilities are critical for successful everyday functioning, and consideration of EF skills is crucial in planning for rehabilitation after treatment for pediatric brain tumors (Aarsen et al., 2009; V. Anderson et al., 2002).

Many models of EF are based largely on research with adult populations. However, it is widely accepted that the frontal lobes, especially areas of the prefrontal cortex, play an important role in supporting EF, and these brain regions continue to develop throughout childhood and into early adulthood (Alvarez & Emory, 2006; V. Anderson et al., 2001; Gilbert & Burgess, 2008). Thus, a four-factor, developmental model of EF was proposed to integrate research and clinical neuropsychological knowledge that applies more readily to childhood and adolescence (Figure 4; P. Anderson, 2002). This model includes: (a)

attentional control, (b) goal setting, (c) cognitive flexibility, and (d) information processing. Although these domains are discrete functions, it is thought that these interrelated domains operate in concert as an overall executive control system in order to complete tasks (P. Anderson, 2002).

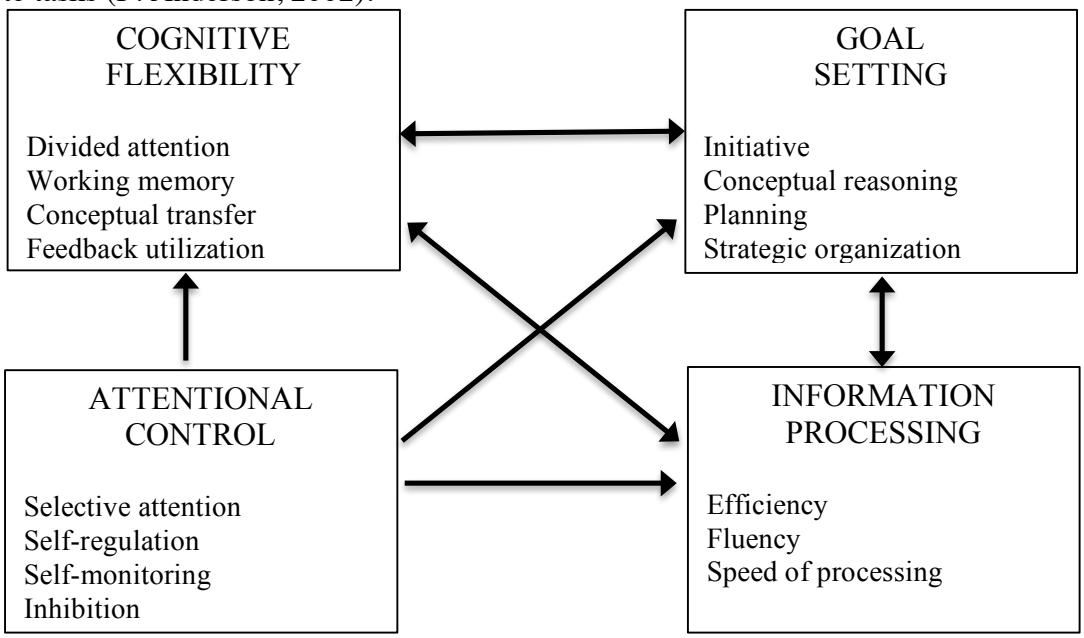

Figure 4: P. Anderson's developmental model of executive functioning.

Attentional control, in this model, greatly influences all other domains of EF. It includes the ability to selectively attend to target stimuli, to inhibit responses when needed, to sustain attention for a prolonged period of time, and to regulate and monitor actions in order to execute plans and achieve goals (P. Anderson, 2002). Individuals with poor attentional control are likely to be impulsive, show difficulties with self-control, struggle to complete tasks, make procedural errors, and subsequently fail to correct those procedural errors.

The goal setting domain in this model includes the ability to develop new ideas, form and initiate ideas and concepts, and develop strategic plans to complete tasks

efficiently (P. Anderson, 2002). Thus, this domain is proposed to include initiative, conceptual reasoning, planning, and strategic organization. Deficits in goal setting can result in limited problem solving abilities due to poor planning and organization, as well as difficulty devising efficient strategies to solve problems, and poor conceptual reasoning.

Cognitive flexibility refers to the ability to learn from mistakes and devise new strategies, divide attention, shift cognitive sets, and concurrently process information from multiple sources (P. Anderson, 2002). This domain includes working memory, divided attention, feedback utilization, and conceptual transfer (or the ability to apply previously learned concepts to novel information or situations). Impairments in cognitive flexibility can be related to high rates of perseveration, or continuing to make the same mistakes repeatedly. Individuals with poor cognitive flexibility can also be rigid, struggle with changes in routines, and struggle to adapt to new demands.

Information processing is conceptually similar to what many cognitive assessments term "processing speed," and refers to an individual's ability to rapidly and accurately process new information (P. Anderson, 2002). This domain is especially reliant on processes such as efficiency, fluency, and speed of processing. Impairments in information processing can lead to decreased output, slowed or delayed responses and reaction times, and hesitancy.

Neurocognitive Functioning and the Cerebellum

Frontal regions of the brain, and in particular the prefrontal cortex, are thought to be the main brain regions related to EF and attention (Alvarez & Emory, 2006; Farrant & Uddin, 2015; Gilbert & Burgess, 2008). However, other research has defined a cerebellar contribution to these processes (Akshoomoff & Courchesne, 1992; Allen et al., 1997; Stoodley & Schmahmann, 2009). Well-known white matter tracts in the brain link the cerebellum to the thalamus and the cerebral cortex, particularly prefrontal areas, via the cerebello-thalamo-cortical pathways, providing further evidence for cerebellar involvement in EF and attention (Law et al., 2011).

A recent meta-analysis conducted by Stoodley and Schmahmann (2008) summarized the findings of 53 functional neuroimaging studies examining cerebellar activation during various neuropsychological tasks. Studies reviewed indicated that working memory paradigms and executive functioning tasks activated the posterior lobes of the vermis and cerebellar hemispheres in particular. The authors concluded that different regions of the cerebellum are responsible for processing information in various domains of functioning. Specifically, they argue for the existence of sensorimotor, emotional, and cognitive regions of the cerebellum, with the cognitive region largely consisting of posterior vermis and hemispheric lobules. Further research has supported the idea that different regions of the cerebellum are involved in more complex mental processes such as EF (Stoodley et al., 2012). Another functional neuroimaging study of age-related declines in processing speed found that variations in cerebellar gray matter in the cerebellum in adults could predict performance on tests of processing speed, but these findings have not been replicated in children or in patients with localized cerebellar damage (Eckert, Keren, Roberts, Calhoun, & Harris, 2010). Research has also suggested that the

cerebellum plays a role in shifting attention rapidly and accurately from one source to another, but that it may not be involved in sustained attention (Akshoomoff & Courchesne, 1992).

Neurocognitive Functioning and Cerebellar Tumors

Lesion and brain tumor studies have linked cerebellar damage to impairment in a variety of attentional and executive functions (Aarsen et al., 2009; Brinkman et al., 2012; Karatekin, Lazareff, & Asarnow, 2000; Knight et al., 2014; Palmer et al., 2013; Riva & Giorgi, 2000; Saury & Emanuelson, 2011; Scott et al., 2001; Vaquero et al., 2008). Research has also compared children with cerebellar tumors to children with tumors in the third ventricle region to examine differential patterns of deficits. King et al. (2004) compared the performance of children with third ventricle tumors to children with tumors of the cerebellum on tasks of verbal memory. The authors concluded that the cerebellar tumor group had poorer performance on a digit span task that could not be explained by other potentially confounding variables (including chemotherapy/radiation exposure and age). A similar study found that children with cerebellar tumors performed worse on a measure of auditory attention than children with third ventricle tumors (Micklewright, King, Morris, & Morris, 2007). Papazoglou et al. (2008) also compared children with third ventricle tumors to children with cerebellar tumors, and found that auditory attention span was the best predictor of adaptive functioning in children with cerebellar tumors but not in children with third ventricle tumors, suggesting that attentional impairments in children with cerebellar tumors could negatively impact their daily living skills. Although these studies did not compare participant performance and cerebellar tumor location, they do provide further evidence for a cerebellar role in executive functioning, specifically auditory attention and auditory working memory.

Research has consistently documented significant deficits in a variety of neurocognitive domains following diagnosis and treatment of cerebellar tumors, but research on the impact of localized cerebellar damage (e.g., from brain tumors in specific

locations) is less prevalent and highly inconsistent. Some researchers hypothesize that these mixed findings may be due to methodological differences (Quintero-Gallego et al., 2011). Additionally, many studies that have looked at cerebellar tumor location and neurocognitive outcomes have done so only as secondary or exploratory analyses, lacked adequate power or sample sizes to draw reliable conclusions, and/or did not control for many potentially confounding variables. For example, Copeland et al. (1999) examined the long-term neurocognitive outcomes of children treated for cerebellar tumors in infancy. Correlations were not significant between any of the neuropsychological domains or behavioral scales and tumor location at the follow-up evaluation. However, over 50% of the patients included in the study had midline tumors, with only three tumors clearly in the right hemisphere and three clearly in the left hemisphere. Although the authors did not report power or effect size estimates, one can conclude that the likelihood of Type II error was higher given the small group sizes used in these comparisons.

Other studies examining cerebellar tumor location and neurocognitive outcomes have included patients with tumors that crossed into various locations within the cerebellum, making it difficult to assess isolated tumor locations (Levisohn et al., 2000). Furthermore, a large amount of research on neurocognitive outcomes after pediatric brain tumors has utilized the Full Scale IQ (FSIQ), which is an amalgam of performance across various cognitive domains. This overall score is often considered "uninterpretable" when a patient shows a significant and unusual difference in performance in various domains that comprise the FSIQ, as it is often not truly representative of a patient's actual abilities across different intellectual domains (Wechsler, 2014). Thus, the clinical and research utility of the FSIQ score in assessing cognitive functioning may be limited. Despite somewhat discrepant findings, the large majority of studies find deficits in at least one

domain of neurocognitive functioning in patients with cerebellar tumors, and some patterns of deficits based on cerebellar tumor location have been identified.

ATTENTION AND CEREBELLAR TUMORS

Deficits in attention are also consistently recorded in survivors of pediatric cerebellar brain tumors, though these results often vary based on the models of attention and the assessment tools utilized in each study. For example, Palmer et al. (2013) found that children with MB showed average performance in the domain of "broad attention" on the Woodcock-Johnson Tests of Cognitive Abilities, Third Edition (WJ-III), but this domain is a composite index comprised of several of the various subcomponents of attention described above and may have masked subtle attentional differences in these patients.

In contrast, many studies have suggested deficits in selective attention in cerebellar tumor patients, especially in the presence of intact sustained attentional abilities (Brinkman et al., 2012; Copeland et al., 1999; Mabbott et al., 2008; Mabbott, Snyder, Penkman, & Witol, 2009; Quintero-Gallego et al., 2011; Reeves et al., 2006; Riva, Pantaleoni, Milani, & Belani, 1989; Steinlin et al., 2003), while other studies have noted no deficits in selective or sustained attention in cerebellar patients (Akshoomoff & Courchesne, 1992; Courchesne et al., 1994). Deficits in shifting attention have also been noted in this population (Akshoomoff & Courchesne, 1992; Brinkman et al., 2012; Copeland et al., 1999; Steinlin et al., 2003). Meanwhile, the cerebellum's contribution to the process of divided attention is much less prevalent in the literature, making it difficult to determine the implications of cerebellar damage on this domain. However, one study of patients with focal cerebellar lesions found that these patients missed significantly more target stimuli and responded to a significantly greater number of non-target stimuli than controls (Gottwald, Mihajlovic,

Wilde, & Mehdorn, 2003). Overall, the literature supports the idea that some aspects of attentional processes are undoubtedly impacted by cerebellar damage, especially selective and shifting attention, while others may remain intact (Ginstfeldt & Emanuelson, 2010).

Though fMRI studies have provided some insight into how distinct cerebellar regions contribute to attentional processes, far fewer studies have examined localized cerebellar damage and attention deficits. However, of the research that has been conducted, some clear trends have emerged. Functional neuroimaging studies have demonstrated, as expected, that the posterior regions of the cerebellum are most active during attention tasks. A study by Allen et al. (1997) found unique activation of the posterior cerebellum independent of motor activity. Akshoomoff and Courchesne (1992) found that children with acquired damage in the posterior regions of the cerebellum were more likely to be impaired on tasks of shifting attention than healthy controls, but noted no significant impairments in selective or sustained attention for the tumor group.

Another study by Courchesne et al. (1994) revealed significant difficulty with shifting attention in patients with posterior cerebellar damage compared to healthy controls, as well as intact sustained attentional abilities. In a similar study, Townsend et al. (2000) also found deficits in shifting attention in patients with posterior vermis damage compared to healthy controls. A study utilizing positron emission tomography found cerebellar vermis activation during divided and shifting attention tasks (Barrett et al., 2003). This same study found that the left cerebellar hemisphere was activated during divided attention tasks while the right cerebellum was activated during shifting attention tasks. However, these studies were limited by their small sample sizes, and many of the attentional tasks administered to patients lacked clear theoretical backing or had poor normative data for comparison. Thus, more research on the effects of cerebellar damage on attentional processes is undoubtedly warranted.

EXECUTIVE FUNCTIONING AND CEREBELLAR TUMORS

The most consistent domain thought to be impacted by cerebellar tumors and their subsequent treatment is the domain of executive functioning. One study of 26 children treated for cerebellar tumors found poor performance on executive functioning and time-based attention tasks (Riva & Giorgi, 2000). Another study of children with cerebellar tumors who had been treated with cranial radiation therapy showed performance on tasks of executive functioning that was well below average (Copeland et al., 1999). A longitudinal examination of neurocognitive functioning in survivors of posterior fossa tumors treated with radiation found significant declines over time on several different measures of executive functioning and working memory (Spiegler et al., 2004).

Other studies have also documented poor performance on measures of executive functioning including processing speed, goal setting (planning) and cognitive flexibility (Aarsen et al., 2009; Brinkman et al., 2012; Docking, Murdoch, & Ward, 2004; King et al., 2004; Knight et al., 2014; Palmer et al., 2013; Saury & Emanuelson, 2011; Spiegler et al., 2004; Steinlin et al., 2003). One interesting and largely consistent finding is that many studies note impaired performance on digit span tasks, which are commonly used to assess patients for working memory deficits (Callu et al., 2009; King et al., 2004; Levisohn et al., 2000; Mak, Tyburski, Madany, Sokołowski, & Samochowiec, 2016; Scott et al., 2001; Steinlin et al., 2003; Vaquero et al., 2008). Deficient performance on verbal working memory tasks is also noted when individuals with focal cerebellar lesions are compared to healthy matched controls (Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Peterburs, Bellebaum, Koch, Schwarz, & Daum, 2010). Another study on executive functioning in patients following cerebellar surgery compared to matched controls showed significantly higher rates of perseverative errors on the Wisconsin Card Sorting Task (WCST), suggesting difficulty with utilizing feedback to shift cognitive sets and achieve a goal (Mak

et al., 2016). This same study documented longer response times on other measures of verbal inhibition, including a Stroop task. Research by Brinkman et al., (2012) found that approximately 55% of adult survivors of MBs in their study had impairments in planning, and approximately 65% showed deficits in shifting attention, even six or more years post-diagnosis and treatment.

Studies on the impact of tumors in different locations within the cerebellum on EF outcomes are less prevalent. Research by Riva and Giorgi (2000), mentioned previously, examined whether neurocognitive outcomes differed in patients based on cerebellar tumor location. Their findings suggested that performance on measures of verbal skills, including verbal working memory, was lower for children with right hemisphere tumors, while nonverbal skills such as visual memory were more impaired in children with left hemisphere tumors. Both groups (right versus left hemisphere) performed poorly on most executive functioning tasks. Specifically, nearly all patients in this study with hemispheric tumors had high rates of perseveration errors on the Wisconsin Card Sorting Test (WCST). Children with tumors of the midline (in the vermis), however, were more likely to show distinct deficits in speech production and articulation, as well as behavioral and affective disturbances that the authors likened to symptoms of autism spectrum disorders (Riva & Giorgi, 2000). Other research has also suggested impairments in cognitive flexibility secondary to damage in the cerebellar hemispheres (Docking et al., 2004; Karatekin et al., 2000). Specifically, studies have linked damage to the posterior lobes of the cerebellar hemispheres to impairments in working memory, planning, set shifting, verbal fluency, abstract reasoning, perseveration, visual-spatial processing, visual memory, logical sequencing, and affective disturbances, while lesions to the anterior lobe were noted to produce only minor changes in some aspects of executive and visual-spatial functioning (Schmahmann & Sherman, 1997).

Regarding the contributions of specific cerebellar hemispheres to EF processes, some research has supported the idea that the right cerebellar hemisphere may be more involved in EF tasks requiring verbal skills than the left hemisphere. A study utilizing theta burst stimulation to interrupt normal cerebellar function examined working memory performance post-stimulation, and found that right hemisphere stimulation led to greater impairments in verbal working memory compared to stimulation of the left hemisphere (Tomlinson, Davis, Morgan, & Bracewell, 2013). Similar studies have confirmed comparable patterns of right hemisphere activation during verbal working memory tasks (Thürling et al., 2012). Studies on children with cerebellar tumors have also found greater impairments in auditory working memory and verbal skills in children with tumors of the right hemisphere, while non-verbal skills appeared to be more impaired in patients with left hemisphere tumors (Gottwald et al., 2004; Levisohn et al., 2000; Puget et al., 2009; Riva & Giorgi, 2000; Scott et al., 2001). However, this research is somewhat limited due to the fact that many working memory paradigms (e.g., digit span and n-back tasks) involve a verbal component. Therefore, it is unclear as to whether the working memory deficits seen in right hemispheric tumors could also be found in patients with left hemispheric tumors performing visual working memory tasks, and more research is needed in this area.

Summary

In summary, both imaging and lesion studies have confirmed that the cerebellum is involved in higher-order processing, and different regions of the cerebellum are implicated in various attention and EF processes (Allen et al., 2011, 1997; Middleton & Strick, 2001; Schmahmann & Pandya, 2008; Stoodley & Schmahmann, 2009; Stoodley et al., 2012). Studies have also identified clear and lasting deficits in attention and EF in survivors of pediatric cerebellar brain tumors (for a review, see Robinson et al., 2013). However, many of these studies have not examined how tumors in specific cerebellar regions can contribute to different patterns of neurocognitive deficits. Of the studies that have examined tumor location, findings have been widely discrepant, likely due to methodological differences and limited sample sizes from which to draw conclusions (Akshoomoff & Courchesne, 1992; Catsman-Berrevoets & Aarsen, 2010; Gottwald et al., 2004; Kirschen et al., 2009; Levisohn et al., 2000; Puget et al., 2009; Riva & Giorgi, 2000; Scott et al., 2001; Townsend et al., 1999). Therefore, more research on how distinct cerebellar tumor location can predict neurocognitive outcomes in survivors of pediatric cerebellar brain tumors is needed.

PROPOSED RESEARCH STUDY

Statement of Problem

Some variables that seem to impact neurocognitive outcomes among survivors of cerebellar brain tumors have been identified, including early age at diagnosis, exposure to chemotherapy, and exposure to cranial radiation (Aarsen et al., 2009; Askins & Moore, 2008; Copeland et al., 1996; Davis et al., 2010; Merchant et al., 2009; Palmer et al., 2013; Ris et al., 2001; Spiegler et al., 2004). However, much less is known about the effects of the location of cerebellar tumors on subsequent neurocognitive outcomes, especially in the domains of attention and EF. Although some work has attempted to address this issue, many of the studies reviewed in this document lacked clear theoretical models to guide the selection of assessment instruments, had limited sample sizes, and had irreconcilable methodological weaknesses. As a result the current state of knowledge surrounding the cerebellum's contribution to EF and attention processes is limited.

It is also possible that the mixed findings surrounding the impact of cerebellar tumors on attention and EF are related to the lack of consideration of tumor location within the cerebellum. As discussed previously, various functional pathways throughout the cerebellum are linked to many different cortical areas involved in processes related to attention and executive functioning (Allen et al., 2005, 1997; Law et al., 2011; Robinson et al., 2013; Stoodley & Schmahmann, 2009; Stoodley et al., 2012). Thus, treating cerebellar tumors as a homogenous group without examining a more precise location of these tumors may limit the ability to uncover subtle yet important differences in neurocognitive outcomes.

Statement of Purpose

The purpose of this proposed study is to examine the impact of cerebellar tumor location on neurocognitive outcomes among survivors of pediatric cerebellar brain tumors. Specifically, the proposed study seeks to determine if cerebellar tumor location can predict neurocognitive outcomes in the domains of attention and EF. Four subcomponents of attention will be examined, including selective, divided, sustained, and shifting attention, based on a theoretical multidimensional model of attention. Additionally, four subcomponents of EF will be examined including cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), and information processing (processing speed) based on Anderson's developmental model of executive function (P. Anderson, 2002). It is hypothesized that cerebellar tumor location (right hemisphere, left hemisphere, vermis) and position (anterior, posterior) will predict neurocognitive outcomes in the domains listed above after controlling for potentially confounding variables including age at diagnosis, exposure to chemotherapy, and exposure to cranial radiation.

Research Questions and Hypotheses

RESEARCH QUESTION 1

Hypothesis 1:

a) Tumor position will account for a significant amount of the variance in performance on a task of selective attention, but tumor location will not. Specifically, it is hypothesized that tumors in the posterior cerebellum will predict poorer performance on a measure of selective attention.

b) Tumor location and position will account for a significant amount of the variance in performance on a task of divided attention. Specifically, it is hypothesized that left hemispheric tumors will predict poorer performance on a measure of divided attention, and that posterior cerebellar tumors will also predict poorer performance on a measure of divided attention.

c) Tumor location and position will account for a significant amount of the variance in performance on a task of shifting attention. Specifically, it is hypothesized that tumors of the right hemisphere will predict poorer performance on a measure of shifting attention. It is also hypothesized that tumors of the posterior cerebellum will predict poorer performance on a measure of shifting attention.

d) Tumor location and position will not account for a significant amount of the variance in performance on a task of sustained attention.

Rationale:

A cerebellar contribution to attentional processes has been established by decades of literature, and studies of patients with cerebellar damage have consistently confirmed attentional deficits in this population (Akshoomoff & Courchesne, 1992; Allen et al., 1997; Brinkman et al., 2012; Copeland et al., 1999; Gottwald et al., 2003; Lassaletta et al., 2015; Mabbott et al., 2008, 2009; Micklewright et al., 2007; Quintero-Gallego et al., 2011;

Reeves et al., 2006; Steinlin et al., 2003; Stoodley & Schmahmann, 2009). The posterior regions of the cerebellum have been implicated in selective and shifting attention (Akshoomoff & Courchesne, 1992; Allen et al., 1997; Courchesne et al., 1994; Townsend et al., 1999). However, unique activation of different cerebellar locations during selective attention tasks has not been confirmed in the literature. Vermis activation has also been noted during divided and shifting attention tasks, as well as right hemisphere activation during shifting attention tasks and left hemisphere activation during divided attention tasks (Barrett et al., 2003). After an exhaustive literature search, only one study reviewed found deficits in sustained attention (Brinkman et al., 2012). None of the aforementioned studies regarding cerebellar tumor location noted deficits in sustained attentional processes.

RESEARCH QUESTION 2

Does cerebellar tumor location (left hemisphere, right hemisphere, vermis) and position (anterior or posterior) predict deficits in executive functioning among survivors of pediatric cerebellar brain tumors, specifically in the subdomains of cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), and information processing (processing speed) after controlling for age at diagnosis and treatment-related variables?

Hypothesis 2:

a) Tumor location and position will account for a significant amount of the variance in performance on a measure of cognitive flexibility (working memory). Specifically, it is hypothesized that right hemispheric tumors will predict poorer performance on a measure of cognitive flexibility, and that posterior cerebellar tumors will predict poorer performance on a measure of cognitive flexibility.

b) Tumor location and position will account for a significant amount of the variance in performance on a task of goal setting (planning). Specifically, it is hypothesized that right or left hemispheric tumors will predict poorer performance on a task of goal setting, and that tumors of the posterior cerebellum will predict poorer performance on a task of goal setting.

c) Tumor location and position will account for a significant amount of the variance in performance on a task of attentional control (inhibition). Specifically, it is hypothesized that right or left hemispheric tumors will predict poorer performance on a task of attentional control, and that posterior tumors will predict poorer performance on a task of attentional control.

d) Tumor location and position will account for a significant amount of the variance in performance on a measure of information processing (processing speed). Specifically, it is hypothesized that right or left hemispheric tumors will predict poorer performance on a measure of information processing, and that posterior tumors will predict poorer performance on a measure of information processing.

Rationale:

Research has consistently documented impairments in EF in survivors of pediatric cerebellar brain tumors (Aarsen et al., 2009; Brinkman et al., 2012; Callu et al., 2009; Copeland et al., 1999; Docking et al., 2004; Gottwald et al., 2004; Holland, 2013; Kahalley et al., 2013; King et al., 2004; Knight et al., 2014; Levisohn et al., 2000; Mak et al., 2016; Palmer et al., 2013; Peterburs et al., 2010; Riva & Giorgi, 2000; Saury & Emanuelson, 2011; Scott et al., 2001; Spiegler et al., 2004; Steinlin et al., 2003; Vaquero et al., 2008). Regarding tumor location and position, studies have found that damage to the posterior lobes of the cerebellum leads to impairment in cognitive flexibility (Docking et al., 2004; Karatekin et al., 2000; Schmahmann & Sherman, 1997). Other studies have suggested that

the right cerebellar hemisphere is more involved in verbal working memory, while the left hemisphere may be more involved in nonverbal processing (Gottwald et al., 2004; Levisohn et al., 2000; Puget et al., 2009; Riva & Giorgi, 2000; Scott et al., 2001; Thürling et al., 2012; Tomlinson et al., 2013). Additionally, connections from the posterior cerebellum to prefrontal brain regions important for EF ability suggest that damage to the posterior region can lead to deficits in performance on EF tasks (Allen et al., 2005, 2011; Middleton & Strick, 2001; Stoodley et al., 2012). Furthermore, studies have suggested that hemispheric damage can lead to significant impairments in EF processes (Schmahmann & Sherman, 1997).

Method

PARTICIPANTS

Participants in this study will include 135 child and adolescent survivors of cerebellar brain tumors, including cerebellar astrocytomas and medulloblastomas. Participants will be recruited through the Childhood Cancer Survivorship Center at the Children's Blood and Cancer Center (CBCC) at Dell Children's Hospital in Austin, Texas. Patients may have undergone any type of treatment for cerebellar tumors, including resection, chemotherapy, and targeted or whole-brain cranial radiation, as treatment type will be controlled for in subsequent analyses. Participants will be within the ages of 8 to 16 so that all participants can be evaluated with the same battery of neuropsychological tests.

Inclusion criteria will be: (i) aged 8 to 16 years old at the time of their participation in the study, (ii) identified as a survivor of a cerebellar brain tumor (CA or MB), as indicated by the child's medical records, (iii) at least one year off treatment, and (iv) fluent in English. Due to the fact that attention problems are frequently documented in children with cerebellar tumors and exposure to cranial radiation, children with diagnoses or reports of attention disorders such as attention-deficit/hyperactivity disorder (ADHD) prior to their tumor treatment will be excluded from this study (King et al., 2004; Levisohn et al., 2000; Micklewright et al., 2007; Steinlin et al., 2003). Participants will be considered eligible to participate if they meet all inclusionary criteria and have pre-operative MRI scans in both the axial and sagittal views available for review in order to determine tumor location and position.

INSTRUMENTS

Participants will be administered a brief neuropsychological assessment including measures of attention and executive functioning. The measures are described below, along with their psychometric properties and purposes in this study.

Attention Measures

Test of Everyday Attention – Children's Version (TEA-Ch). The Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999) is a children's adaptation of the Test of Everyday Attention (TEA), and is designed to measure attentional capacities in children aged 6:0 to 15:11. The full TEA-Ch is comprised of nine subtests and takes approximately 55 to 60 minutes to administer. The TEA-Ch also has a screener comprised of only four subtests that assesses four major domains of attention (selective, divided, sustained, and shifting), which takes approximately 20-25 minutes to administer. The TEA-Ch was normed on a sample of 293 Australian children and adolescents with approximately equal numbers of males and females. Estimates of test-retest reliability coefficients across the normative sample ranged from 0.57 to 0.87 for the various TEA-Ch subtests. A structural equation modeling study of the TEA-Ch conducted on the normative sample yielded a three-factor model of attention including sustained attention, selective attention, and attentional control/switching (Manly et al., 1999).

For the purposes of this study, the four-subtest screener will be administered, consisting of the subtests *Sky Search, Score!, Creature Counting (Accuracy), and Sky Search DT*. *Sky Search* is a measure of selective attention in which a subject is required to filter through irrelevant information while searching for specific targets, thus rejecting or inhibiting distractors. Reported test-retest reliability for *Sky Search* was 0.75. *Score!* is a measure of sustained attention, where a child is required to listen to and count the number

of "scoring sounds" on an audio recording on ten trials, each of which varies in total length, the number of sounds presented, and the length of time between stimulus presentation (scoring sounds). Reported test-retest reliability for this subtest was 0.76. *Creature Counting* requires a child to switch between the relatively simple activities of counting upwards and downwards according to visual cues, and is a measure of switching attention. This subtest generates two scores, one for accuracy and one for speed (timing); the accuracy score will be utilized in this study to provide a measure of attention that is less dependent on processing speed demands. The reported test-retest reliability for *Creature Counting* was 0.71. *Sky Search DT* is a measure of sustained divided attention that requires a child to search for relevant stimuli (as in *Sky Search*) while also counting the number of "scoring sounds" presented from an audiotape (as in *Score!*). The test-retest reliability reported for this subtest was 0.81.

Executive Functioning Measures

Delis-Kaplan Executive Functioning System (D-KEFS). The Delis-Kaplan Executive Functioning System (D-KEFS) is a comprehensive assessment of executive functioning designed for children and adults aged 8 to 89 years. The D-KEFS was standardized on a random sample of 1,750 individuals that was stratified to match US census data on sex, race/ethnicity, years of education, and geographic region. The full battery of the D-KEFS contains nine subtests and takes approximately 90 minutes to administer. This study will utilize two D-KEFS subtests, Tower and Color-Word Interference.

The D-KEFS Tower subtest is a widely accepted measure of spatial planning and reasoning (Baron, 2004; Delis, Kaplan, & Kramer, 2001). This task requires an individual to move different sized discs across three pegs to build towers using the fewest number of

moves possible. Though the subtest generates several scores, the Total Achievement score will be utilized for the purposes of this study. The reported internal consistency of this measure for children aged 8 to 16 ranged from 0.43 to 0.84. The D-KEFS Color-Word Interference test is designed to measure verbal inhibition (Baron, 2004; Delis et al., 2001). It is a modified version of the Stroop test, which requires an individual to inhibit a more automatic verbal response (reading the word) to generate a conflicting response (naming the ink colors instead of reading the words). A later trial requires the child to switch back and forth between naming the dissonant ink color and reading the conflicting word. This subtest also generates several scores, but the scaled score from Trial 3 (Inhibition) will be utilized for the purposes of this study. The reported test-retest reliability coefficient for this subtest for children aged 8 to 16 was 0.90.

Wechsler Intelligence Scale for Children – 5th Edition (WISC-V). The Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; (Wechsler, 2014) is a widely utilized measure of cognitive functioning designed for use with children between the ages of 6:0 and 16:11. It consists of fifteen subtests, ten of which are in the core battery and five that are supplemental. The core battery takes approximately 60 minutes to administer, and yields a measure of global cognitive ability, the Full Scale IQ (FSIQ) that is derived from seven of the ten subtests in the core battery. The WISC-V also yields a variety of primary and ancillary index scores that are used to classify an individual's cognitive abilities in several domains, including the Verbal Comprehension Index (VCI), the Visual Spatial Index (VSI), the Working Memory Index (WMI), the Fluid Reasoning Index (FRI), and the Processing Speed Index (PSI).

This study will utilize four subtests of the WISC-V, two that make up the PSI and two that make up the WMI. The two subtests that comprise the PSI are Symbol Search and Coding. Symbol Search requires an individual to quickly visually scan a group of

stimuli printed on a page and mark whether or not a target stimulus is present. The reported test-retest reliability coefficient for this subtest is 0.81. The Coding subtest requires a child to copy a set of symbols matched with numbers or letters within a given time limit. The reported test-retest reliability coefficient from the normative sample for this subtest was 0.82. These two subtests will be combined to create an overall PSI composite score, which will be utilized in the analyses for this study. The two subtests that make up the WMI are Digit Span and Picture Span. Digit Span, a verbal working memory task, consists of three tasks, Digit Span Forward (DSF), Digit Span Backward (DSB), and Sequencing (SEQ). These tasks require a child to repeat a series of orally presented digits, first forward (DSF), then backward (DSB). SEQ requires the child to listen to a series of numbers, and then repeat them back in numerical order. Performance on these tasks is combined to yield a single score for Digit Span. The reported internal consistency for this subtest from the normative sample was 0.91. Picture Span, a visual working memory task, requires a child to view a set of pictures and choose those pictures in the order they were presented from an array of various images. The reported internal consistency for this subtest was 0.85. Digit Span and Picture Span will be combined to yield an overall WMI composite score, which will be utilized in the analyses for this study.

PROCEDURE

Tumor Location

Cerebellar tumor location will be verified by MRI scans in the child's medical record. Both the primary author of this document as well as a neuropsychologist with expert knowledge in cerebellar anatomy will review these scans. Only participants with both axial and sagittal images of their tumors available will be included for the purposes of this study.

Tumors will be classified on two dimensions, location and position. Possible tumor locations of interest in this study are those in the left cerebellar hemisphere, the right cerebellar hemisphere, or the vermis, and possible positions are anterior and posterior. Hemispheric tumors will be considered anteriorly positioned if they occur anterior to the primary fissure, and will be considered posteriorly positioned if they occur posterior to the primary fissure. Tumors in vermis lobules I through V will be considered anteriorly positioned, and tumors in vermis lobules VI through IX will be considered posteriorly positioned. To summarize, tumor classification will be as follows: (1) Location (vermis, left hemisphere, or right hemisphere) and (2) Position (anterior or posterior). Brain tumors are often unpredictable and may not be neatly positioned within the boundaries specified above. As such, tumors will be classified by position and location if at least 90% of the tumor's total volume occurs in a position and/or location. Tumor volume will be abstracted from pathology reports in the patient's medical record.

Approval by Human Subjects Committee

This study will be conducted in compliance with ethical standards set forth by the American Psychological Association and the University of Texas at Austin. As such, all research materials and procedures will be approved prior to the start of data collection by the Departmental Review Committee within the Department of Educational Psychology and by the Institutional Review Board of the University of Texas at Austin.

Recruitment of Participants

Participants for the experimental group will be recruited through the Children's Blood and Cancer Center at Dell Children's Medical Center in Austin, Texas. Children identified as having had a cerebellar brain tumor (cerebellar astrocytoma or

medulloblastoma) by their oncologist or via their medical record that meet the inclusionary criteria will be invited to participate.

Consent

The researcher will provide the parents or guardians of participants with a copy of the consent form, and will be given an opportunity to discuss any concerns. All participation in this study will be voluntary, and participants will be able to discontinue their participation at any time. Child participants will be given the opportunity to ask questions about the study, and will be given an assent form to sign upon a discussion of study procedures.

Data Collection

Children whose parents have given consent for participation, who assent to participate in the study, and who meet inclusion and eligibility criteria for this study will be participants. Informed consent and assent will be obtained, and the investigator will schedule an appointment with the parent or guardian of the child to participate in the neuropsychological evaluation. Children who are due for a neuropsychological evaluation or re-evaluation as part of their routine medical care will receive a full neuropsychological evaluation, while children who are not due for an upcoming evaluation or re-evaluation will be administered only the short battery that will be utilized in this study. A full neuropsychological evaluation will take approximately 330 to 400 minutes including the study measures, while the research-only battery should last approximately 90 minutes. Measure of interest in this study will be administered first to all participants to avoid issues related to fatigue in children receiving a full neuropsychological evaluation. All evaluations will take place one-on-one in a quiet, private room in the Children's Blood and

Cancer Center (CBCC) at Dell Children's Medical Center (DCMC) in Austin, Texas. Children will be given breaks as needed during testing.

Data Analyses and Expected Results

The purpose of this study is to examine the relationship between cerebellar tumor location and neurocognitive functioning among survivors of pediatric brain tumors. Data will be analyzed using a series of multiple regression analyses.

Preliminary Analyses

The independent variables in this study (chemotherapy exposure, radiation exposure, and age at diagnosis) are consistently indicated in the literature to impact neurocognitive functioning, but differential functioning based on tumor type and biological sex has not yet been confirmed. In order to determine the need to control for the effect of these variables on the outcome variables of interest, *t*-tests and chi-square analyses will be used to examine whether the performance of the distinct tumor groups (CA, MB) or sexes (male, female) is significantly different on each of the variables of attention and EF utilized in this study. Separate independent samples *t*-tests comparing age at diagnosis across the two tumor types and two sexes, along with chi-square analyses of independence for categorical variables (chemotherapy exposure, radiation exposure), will be conducted to ensure that there are no significant relationships between tumor type or sex and the other independent variables of interest in this study. Finally, chi-square analyses will compare tumor type and sex with tumor location to ensure that these variables are not confounded. Comparisons will be considered significant at an alpha level of 0.20 in order to ensure that confounding relationships between variables are not overlooked.

A power analysis was conducted using G*Power software to determine the number of participants needed to detect a significant effect (Faul, Erdfelder, Buchner, & Lang, 2009). A power analysis for detecting the significance of a moderate effect size with a power of 0.80 at an alpha of 0.01 with six predictor variables (assuming there is no need to

control for tumor type or sex) indicated a need for 135 participants. A Bonferroni correction applied at the level of each outcome variable suggested an alpha level of .0125. An alpha level of 0.01 was chosen as a conservative cutoff for determining statistical significance in order to correct for multiple comparisons.

Descriptive statistics, including means, standard deviations, ranges, and minimum and maximum values will be computed and analyzed for each variable. Variables will be checked for normality and data will be examined for any potential outliers. Linearity will be determined by examining scatterplots. Normal distribution of residuals will be confirmed using a residual and predicted value plot.

TESTS OF RESEARCH QUESTIONS

Hypothesis 1:

a) Tumor position will account for a significant amount of variance in performance on a task of selective attention after controlling for age at diagnosis and treatment-related variables, while tumor location will not. It is hypothesized that tumors in the posterior region of the cerebellum will predict poorer performance on a measure of selective attention.

b) Tumor location and position will account for a significant amount of the variance in performance on a task of divided attention after controlling for age at diagnosis and treatment-related variables. It is hypothesized that tumors of the left cerebellar hemisphere will predict poorer performance on a measure of divided attention. It is also hypothesized that tumors of the posterior cerebellum will predict poorer performance on a measure of divided attention. An interaction is hypothesized, where it is expected that posterior left hemispheric tumors will explain a significant

amount of variance in performance on a measure of divided attention, above and beyond that accounted for by demographic or treatment-related variables.

c) Tumor location and position will account for a significant amount of the variance in performance on a task of shifting attention after controlling for age at diagnosis and treatment-related variables. It is hypothesized that tumors of the right hemisphere will predict poorer performance on a measure of shifting attention. It is also hypothesized that tumors of the posterior cerebellum will predict poorer performance on a measure of shifting attention. An interaction is hypothesized, where it is expected that tumors in the posterior regions of the right hemisphere will explain a significant amount of variance in performance on a measure of shifting attention, above and beyond that accounted for by demographic or treatment-related variables.

d) Tumor location and position will not account for a significant amount of the variance in performance on a task of sustained attention beyond that accounted for by age at diagnosis and treatment-related variables.

Hypothesis 2:

a) Tumor location and position will account for a significant amount of the variance in performance on a measure of cognitive flexibility (working memory) after controlling for age at diagnosis and treatment-related variables. It is hypothesized that tumors of the right cerebellar hemisphere will predict poorer performance on a measure of cognitive flexibility. It is also hypothesized that tumors of the posterior cerebellum will predict poorer performance on a measure of cognitive flexibility. An interaction is hypothesized, where it is expected that posterior right hemispheric tumors will explain a significant amount of variance in performance on a measure

of cognitive flexibility above and beyond that accounted for by demographic or treatment-related variables.

b) Tumor location and position will account for a significant amount of the variance in performance on a task of goal setting (planning) after controlling for age at diagnosis and treatment-related variables. It is hypothesized that right or left hemispheric tumors will predict poorer performance on a task of goal setting. It is also hypothesized that posterior cerebellar tumors will predict poorer performance on a task of goal setting. An interaction is hypothesized, where it is expected that posterior hemispheric tumors (right or left) will explain a significant amount of variance in performance on a task of goal setting above and beyond that accounted for by demographic or treatment-related variables.

c) Tumor location and position will account for a significant amount of the variance in performance on a task of attentional control (inhibition). It is hypothesized that hemispheric tumors (right or left) will predict poorer performance on a task of attentional control, and that posterior tumors will predict poorer performance on a task of attentional control. An interaction is also hypothesized, where it is expected that posterior hemispheric tumors (right or left) will explain a significant amount of variance in performance on a task of attentional control above and beyond that accounted for by demographic or treatment-related variables.

d) Tumor location and position will account for a significant amount of the variance in performance on a measure of information processing (processing speed). It is hypothesized that hemispheric tumors (right or left) will predict poorer performance on a measure of information processing, and that posterior tumors will predict poorer performance on a measure of information processing. An interaction is also hypothesized, where it is expected that posterior hemispheric tumors (right

or left) will explain a significant amount of variance in performance on a measure of information processing above and beyond that accounted for by demographic or treatment-related variables.

DISCUSSION

Limitations

The proposed study has several limitations, including the cross-sectional, as opposed to longitudinal, nature of the study design that does not follow children from diagnosis through survivorship. This makes it difficult to determine whether observed deficits would change or improve over time (Scott et al., 2001). Furthermore, participants cannot be randomly assigned to tumor locations for obvious reasons. Together, these limitations preclude the ability to infer causation from the results.

Another potential limitation of this study is related to participant treatment exposure, wherein this study is only controlling for exposure to cranial radiation as a dichotomous variable. Research has demonstrated differential impacts of cranial radiation based on radiation dosages, where lower doses of radiation have been linked to better neurocognitive outcomes (Grill et al., 1999). As such, it is possible that grouping patients with high- and low-dosage radiation exposure may conceal differences in neurocognitive outcomes between these groups with relation to tumor location/position. However, this decision was made because a central research question of this study was not related to the differential impact of radiation dosages, and any amount of cranial radiation has lasting effects on neurocognitive functioning (Ris et al., 2001; Spiegler et al., 2004; Steen et al., 2001).

The proposed study is also limited by the fact that research has shown attention and EF to be at least somewhat impacted by an individual's intellectual functioning(Jurado & Rosselli, 2007; Schweizer, Moosbrugger, & Goldhammer, 2005). It is possible that intellectual functioning could account for some of the variability in performance on executive functioning and attention tasks, and this study does not propose the use of an IQ

assessment. However, some authors have argued against using IQ as a covariate in studies of neurocognitive functioning because it does not meet the requirements for a covariate and could inadvertently overcorrect findings (Dennis et al., 2009). Thus, associations between intellectual functioning and higher-order cognitive processes such as EF and attention may not be ideal from a statistical standpoint, but from a practical and clinical standpoint removing the effects of IQ on EF and attention could ultimately misrepresent individuals' actual abilities in these areas.

Summary and Implications

The proposed study seeks to fill a large gap in the literature on neurocognitive outcomes following treatment for cerebellar brain tumors. Specifically, it seeks to understand how localized cerebellar damage, as assessed by including participants with tumors in varying locations and positions within the cerebellum, can impact later neurocognitive outcomes, specifically in the domains of attention and EF. It is expected that differential tumor locations and positions, as verified by patients' pre-operative MRI scans, will predict post-treatment functioning in the domains of attention and EF in survivors of pediatric brain tumors. Attention and EF are important for school functioning and daily living skills in this population, and a deeper understanding of the impact of cerebellar tumor location on neurocognitive functioning could lead to more targeted post-treatment therapies for these children (Papazoglou et al., 2008). Consequently, this study could have important implications for survivors and their families.

Another possible contribution of this study to the literature is its potential for revealing more about the functionality of the cerebellum, which is still not clearly understood. This study could offer a more detailed examination of localized cerebellar damage and neurocognitive outcomes than is currently available in the literature. This could facilitate an increased understanding of the highly complex circuitry of this enigmatic brain region.

Future research could also expand upon the current proposed study by gathering pre- and post-treatment assessments of attention and EF, as well as follow-up assessments at designated intervals for several years after treatment. This would allow an investigation into how these processes change over time. Additional research could examine the psychosocial factors related to neurocognitive outcomes after treatment for pediatric brain

tumors, as some research has suggested better outcomes for children with more positive family functioning (Carlson-Green, Morris, & Krawiecki, 1995).

This study has the potential to be one of the first steps in a line of important research on neurocognitive outcomes following localized cerebellar damage from pediatric brain tumors. The results of this study may encourage researchers to replicate these methods, further building the knowledge base of the functionality of the cerebellum and its contributions to human behavior. Increased understanding about how specific cerebellar brain tumor locations impact attention and executive functioning could contribute greatly to the development of targeted therapies to improve functional outcomes for children with cerebellar tumors.

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